PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 143019.8SB	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL 03/00205	International filing date *(day/month/year)* 13.03.2003	Priority date *(day/month/year)* 13.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/00		
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 29.09.2003	Date of completion of this report 19.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Koessler, J-L Telephone No. +49 89 2399-7217

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL 03/00205

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 4, 7-20	as originally filed
3, 3a, 5, 6	received on 19.04.2004 with letter of 19.04.2004

Claims, Numbers

1-14	received on 19.04.2004 with letter of 19.04.2004

Drawings, Sheets

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-14 (partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-14 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The present application had only a partial search report drawn up because of lack of unity. Furthermore, only two examination fees were paid. Hence, the present communication relates only to the subject-matter indicated by the applicant i.e. compound of formula I wherein n is 1, X is NHR, X' is H and Y is OR1, the use thereof for the preparation of a medicament and a pharmaceutical composition comprising said compound (claims 1-14 partially) and compounds of formula I wherein n is 1, X is NHR, X' is CH2OH and Y is OR1, the use thereof for the preparation of a medicament and a pharmaceutical composition comprising said compound (claims1-14 partially). The Applicant is invited to restrict the claims to said subject-matter and to adapt the description accordingly.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Cited documents**

Reference is made to the following documents:

D1: LAVEY B J ET AL: 'Catalytic antibody mediated hydrolysis of paraoxon' JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 61, no. 21, 18 October 1996 (1996-10-18), pages 7633-7736, XP002244436 ISSN: 0022-3263

D2: LAVEY B J ET AL: 'Antibody catalyzed hydrolysis of a phosphotriester' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 13, 9 July 1996 (1996-07-09), pages 1523-1524, XP004175745 ISSN: 0960-894X

D3: WO9945016

2. Amendments (Art. 34(2) PCT)

The Applicant restricted the subject-matter of new claim 1 to compounds of formula (I) wherein n is 1. Nevertheless he did not further restrict the subject-matter of claim 1 concerning the definition of X, X' and Y (see item III).

The Applicant deleted the following disclaimer: X = X' = H and n = 0, Y is not OR_1 wherein R_1 is H, alkyl or aryl which do no longer fall under the scope of new claim 1 (cf n = 1).

The Applicant however introduced to new disclaimers:
- X and X' can not be at the same time H. The Applicant introduced this to exclude compound 7 of D1 and compound 6 of D2 (which are in fact the same compound). Accordingly, the Applicant deleted compound i, j from original claim 5 and 12. This disclaimer is useless since this compound does not fall under the scope of the present examination report (see item III). The Applicant is reminded that he did not pay the search fees for the invention(s) wherein X and X' is H and hence this subject-matter need not be the subject of an international preliminary examination (R. 66(1)e).
- when X is NH-R where R is a linear or branched acyl Y is not OR_1 for R_1 being a 4-nitrophenyl. This disclaimer has been introduced to exclude compound 8 of D1 and compound 6 of D2 (which are in fact the same compound). This disclaimer is not acceptable under Art. 34(2) PCT. The subject-matter of a disclaimer should be strictly limited in scope in order to exclude only the accidental novelty destroying compound(s). This disclaimer could be acceptable if R is Ac. Hence, new claim 1 is not acceptable under Art. 42(2) PCT.

The Applicant adapted the corresponding part of the description (p. 5, 6) to new claim 1.

The Applicant deleted "substantially as described in the specification from claim 13.

New pages 3 and 3a wherein the Applicant pretends having acknowledged D1-D3 are certainly erroneous.

3. Novelty (Art. 33(2) PCT)

The present application relates to 1,3-cyclic propanediol phosphate derivatives pharmaceutical composition thereof and the use of said derivatives as cell stimulants.

D1 and D2 relate to antibody catalyzed hydrolysis of a phosphotriester.

D3 is directed towards prodrugs of substituted cyclic 1,3-propanyl phosphate, phosphonate and phosphoramidate ester compounds which in their active form have a phosphate, phosphonate, or phosphoramidate group, to their preparation, to their synthetic intermediates, and to their use. D3 does not describe compounds of formula (I) wherein X' is CH_2OH. Although the rest of the compounds claimed in the present application fall under the scope of the claims of D3, this document does not describe explicitly any compounds which fall under the scope claim 1 of the present application.

None of the cited documents describe explicitly a compound which falls under the scope of new claim 1. Hence, the present application meets the requirements of Art. 33(2) PCT because the subject-matter of claims 1-14 is not novel.

4. Inventive step (Art. 33(3) PCT)

The closest prior art is considered to be document D3.

The problem underlying the present application is to be regarded as to provide alternative cyclic glycerophosphate derivatives, pharmaceutical compositions thereof and the use of said derivatives for the preparation of a medicament.

The Applicant in his reply argues that the compounds of D3 have a polyphosphate group. But D3 recites (claim 1): "M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$ is biologically active". This does not mean that M possess such a mono, di, or triphosphate group. However the compound of D3 are prodrugs for treating cancer (claim 243), viral infections (claim 248), liver fibrosis

(claim 256), hyperlipidaemia (claim 257) and parasitic infections (claim 260) whereas the compounds of the present application are useful in the treatment of diseases or deficiencies related to neural cell activity.

None of the cited documents nor a combination of the teaching would fairly suggest that the compounds of formula (I) are neural cell stimulants.

Therefore, the present application meets the requirements of Art. 33(3) PCT because the subject-matter of claims 1-14 is inventive.

5. Industrial applicability (Art. 33(4) PCT)

The subject-matter of claims 1-14 is considered to be industrially applicable.

6. Clarity (Art. 6 PCT)

The embodiments of the invention described on pages 15 (examples 10 and 11) do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

The applicant is requested to remove the inconsistency by deleting the "excess" subject-matter from the description or by indicating in the description that the embodiments concerned do not form part of the invention but represent background art that are useful for understanding the invention (see the PCT Guidelines, III-4.3).

7. Other defects of the application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.